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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JUN 7 2005

Clark Bishop, M.D.
Utah Valley Institute of Cystic Fibrosis
1034 North 500 West
Utah Valley Regional Medical Center
Provo, Utah 84604

Ref: 05-HFD-45-0601

Dear Dr. Bishop:

Between January 27 and 30, 2004 and on February 2 and 5, 2004, Mr. Thaddeus M. Steinke representing the Food and Drug Administration (FDA), conducted an investigation regarding an allegation that you conducted a clinical study using [] in patients with cystic fibrosis. Mr. Steinke reviewed the conduct of your clinical investigation entitled: "Treatment of Cystic Fibrosis with Reduced [] involving the investigational drug [] for which you served as the sponsor and clinical investigator. Mr. Steinke presented and discussed Form FDA 483, Inspectional Observations, with you at the conclusion of the inspection. This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

Based on our evaluation of the inspection report, the documents submitted with the report, other pertinent information obtained by the Agency, your January 27, 2004 and March 10, 2004 written correspondences addressing item #1 on Form FDA 483, and in consultation with the Center for Drug Evaluation and Research's Division of Pulmonary and Allergy Drug Products (DPADP), we conclude that you violated the Federal, Food, Drug, and Cosmetic Act (the Act) and FDA regulations governing the use of investigational new drugs, by initiating a clinical investigation subject to 21 CFR Part 312 without an investigational new drug application (IND) in effect and by failing to meet the obligations of a sponsor and an investigator under applicable regulations, as indicated below.

1) FAILURE TO CONDUCT THE STUDY UNDER AN IND [21 CFR 312.20].

FDA regulations require that a sponsor submit an IND to the FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug [21 CFR 312.20(a)] and have an IND in effect before the investigational drug is administered to

study subjects [21 CFR 312.40(a)(1)]. A sponsor is a person who takes responsibility for and initiates a clinical investigation [21 CFR 312.3(b)]. A clinical investigation is defined as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects” [21 CFR 312.3(b)]. The definition of a drug includes, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man” [21 U.S.C § 321(g)(1)(B)]. Our investigation indicates that you initiated and were responsible for the conduct of a clinical investigation designed to determine whether [] for inhalation, an investigational drug, is an effective treatment for cystic fibrosis. Accordingly, you were the sponsor and should have had an IND in effect before proceeding with the above-referenced study.

Our records indicate that, on May 20, 2002, you submitted an IND (IND []) for [] inhalation to the FDA (to the Division of Pulmonary and Allergy Drug Products (DPADP) in the Center for Drug Evaluation and Research). During a June 17, 2002 teleconference, you were advised by DPADP that, for safety reasons, your proposed study could not be allowed to proceed (a memorandum of this teleconference was also faxed to you on June 25, 2002). When so advised, you requested that your application be withdrawn (request confirmed by written correspondence faxed to DPADP on June 17, 2002). On that same day, notwithstanding the safety concerns communicated to you by DPADP, and without an IND in effect, you initiated the clinical investigation in which you administered [] to children and adolescents with cystic fibrosis. Over the course of the study you enrolled 19 subjects, 10 in the [] treatment group and 9 in the control (placebo) group.

In a letter dated July 12, 2002, DPADP confirmed that your IND was effectively withdrawn and reiterated in detail the deficiencies in your IND submission and the additional data and information that would be required for DPADP to make a determination about whether the study would be safe to proceed. The letter further advised that you must inform your IRB of the safety reasons for withdrawal of the IND and notify DPADP should you choose to conduct a clinical investigation involving the use of [] in the future:

We remind you that you must notify any clinical investigators and all reviewing IRBs of the withdrawal of this IND and of the safety reasons for this withdrawal. We remind you that any unused drug must be disposed of properly. The withdrawal procedure is now complete. If this drug is again subjected to clinical investigation, it is required that we be notified. This may be done by submitting a new IND.

In your written responses to the Form FDA 483 dated January 27, 2004 and March 10, 2004, you stated, “[a]fter a telephone conference with FDA, we decided to withdraw the application for the IND. During the conference, FDA staff members suggested that we needed additional animal data to justify obtaining the IND. The FDA staff members did not tell us not to conduct the study. Furthermore, I never told them that

we were not going to proceed, but the issue was never explicitly discussed.” However, contemporaneous minutes of the June 17, 2002 telephone conference, dated June 25, 2002 and provided to you, contradict your assertion. In any event, your explanation does not provide a justification for conducting the study in light of the significant safety concerns communicated to you by DPADP. You also claimed that you did not receive DPADP’s July 12, 2002 letter until December of 2003. You stated that the letter was discovered in the office of a co-investigator [] who was out on maternity leave at the time the letter arrived. Again, even if you were unaware of the contents of this letter, you had been previously advised of FDA’s significant safety concerns with respect to your study in the telephone conference of June 17, 2002 and in the memorandum of that telephone conference faxed to you on June 25, 2002. Lastly, you have argued that you were advised by counsel that your study did not require an IND. Regardless of the advice you may have received, you bear responsibility for compliance with the law. Further, ignorance of these requirements would not explain your decision to undertake the study in light of the significant safety concerns communicated to you.

2) FAILURE TO PROTECT THE RIGHTS, SAFETY AND WELFARE OF SUBJECTS UNDER YOUR CARE [21 CFR 312.60].

Our investigation indicates that, for purposes of the IND regulations, you were an investigator, as well as a sponsor, for the above-referenced clinical trial. An investigator is defined as “an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject)” [21 CFR § 312.3(b)]. Available records indicate that you conducted a clinical investigation in which you enrolled 19 subjects, and randomized them to receive either [] for inhalation or a placebo control. Among other things, an investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator’s care. You failed to adequately protect the rights, safety, and welfare of the children and adolescents with cystic fibrosis who you enrolled in the above-referenced clinical study.

- a. There were not sufficient human study data, previous human experience, or pre-clinical data to conclude that the dose, duration, and route of administration of [] for inhalation in the proposed study population would not expose subjects to an unreasonable and significant risk of harm.

In the IND you submitted to DPADP on May 20, 2002 (IND []) you proposed to conduct a two-part study of [] for inhalation in the treatment of cystic fibrosis—a short safety study in six normal children followed by a placebo-controlled study in at least 20 children with cystic fibrosis. During a telephone conference on June 17, 2002, you were advised by DPADP that available safety data were not adequate to support administering [] by inhalation to a pediatric population or administering multiple doses to humans. You were specifically advised that single dose studies in adults included in your

submission did not contain sufficient safety data concerning the effects of [] on pulmonary function and that your submission lacked the animal toxicity data needed to initiate multiple dose studies in humans or to administer single doses in excess of 600 mg. Despite DPADP's concern, you enrolled 19 children and adolescents with cystic fibrosis and administered subjects 66mg/kg/day (1500-4500 mg/day) of [] for up to 8 weeks.

- b. There were not sufficient chemistry, manufacturing, and controls data and information to conclude that the dosage form of [] used in the study would not expose subjects to an unreasonable and significant risk of harm.

Your submission lacked sufficient information about the identity, purity, quality, strength, and stability of [] for inhalation capsule. For example, you did not provide information on the structure elucidation of [] method of preparation/manufacture of the drug substance, including the reagents, solvents and catalysts used; appropriate method to confirm the identity of the drug substance (e.g., infrared spectroscopy, high-pressure liquid chromatography); provide appropriate methods to support the purity and to establish the impurity profile of the drug substance; or provide information to support the stability of the drug substance during, and beyond, the study period.

- c. The protocol lacked sufficient detail concerning inclusion/exclusion criteria and in-study safety assessments to ensure that risks to subjects were minimized.

The protocol did not sufficiently describe the clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of [] in human subjects and to minimize risk [21 CFR 312.23(a)(6)(iii)(g)]. Your protocol did not provide for adequate safety monitoring. Specifically, your protocol lacked adequate provisions for monitoring adverse events, serious adverse events, withdrawals due to adverse events, exacerbations, hospitalizations, vital signs, physical examinations, laboratory studies, and electrocardiograms, and did not include specific rules for discontinuation of patients from the study. In addition, you were specifically advised by DPADP that post-dose pulmonary function tests (PFTs) alone were not adequate to assess subject safety and that pre-dose PFTs should be done as well.

- d. You failed to follow specific criteria in your protocol intended to minimize risks to study subjects.

Your protocol specified that subjects with a positive culture for mucoid *Pseudomonas aeruginosa* within the past 5 years were to be excluded. Notwithstanding this criterion, you enrolled seven subjects (9, 10, 12, 13, 14, 16, and 22) who had a positive mucoid *Pseudomonas aeruginosa* culture within 5 years of enrollment into the study.

Your protocol also specified that to be included in the study, subjects had to have a “clinical diagnosis of cystic fibrosis, as confirmed by positive sweat chloride test.” Our investigation found no documentation to indicate that subjects’ cystic fibrosis diagnoses were confirmed by a sweat chloride test.

These departures from the protocol apparently occurred without provision of the required notice to the IRB of such a change in the research [21 CFR 312.66]. Accordingly, not only did these violations directly increase the level of risk associated with the study, they also appear to have prevented the IRB from effective oversight, potentially further exacerbating the risks posed to study subjects.

- e. Your protocol included specifications that increased the risks to study participants.

For example, your protocol specified that distilled water, rather than sterile water, be used to prepare the [] and placebo solutions for inhalation via a nebulizer. Use of distilled water posed an increased risk of infection from waterborne pathogens to already susceptible children and adolescents. In addition, you allowed subjects from out of state to be enrolled in the study without adequate oversight.

- f. You continued to make investigational drug available to study subjects after the completion of the study.

In a letter to the subjects dated August 19, 2002, you offered samples of [] for inhalation to subjects randomized to the placebo group for use after their study participation ended. In the letter, you stated the following, “[i]f you were on Placebo, you may try [] We will provide you with samples.”

3) FAILURE TO PROMPTLY REPORT TO THE IRB ALL UNANTICIPATED PROBLEMS INVOLVING RISK TO HUMAN SUBJECTS OR OTHERS [21 CFR 312.66].

An investigator is required to promptly report to the IRB all unanticipated problems involving risk to human subjects or others (21 CFR 312.66). Protocols typically include discussion of anticipated problems involving risks to human subjects or others; however, your protocol did not adequately describe any anticipated problems or risks to subjects. Since you provided the IRB no information to assess the likelihood that subjects would experience an anticipated problem or category of problems, you should have reported all problems experienced by subjects to the IRB as potential adverse events. Our investigation found, however, that you failed to promptly report multiple adverse events experienced by subjects. Specifically, in your September 6, 2002, “Continuing Review of Research” report to the IRB, you indicated that the study was closed to enrollment, that the subjects were being

followed, and that you did not receive any reports of adverse drug reactions. In addition, in the section of that report entitled “Current Risk-Benefit Assessment” you discussed potential benefits (“I believe this will prove a useful treatment of CF in the future”) but failed to include a review of reported adverse events documented in the patient diaries []CF Study Daily Logbook). The following are examples of adverse events that were reported by the subjects but not reported by you to the IRB:

Subject No.	Treatment Arm	Approximate Treatment Dates	Date of Adverse Event Reported in Patient Diaries
1	Placebo 7 caps./day	7/1/02-9/3/02	7/16/02-Dosage reduced due to nose and throat irritation 7/20/02-cold 8/23/02-flu
2	Placebo 7 caps./day	7/4/02-8/21/02	7/15/02-headache 7/20/02-bronchospasm 7/25/02-sore throat, headache 7/27/02-croupy 8/7/02-dizzy
3	[] 4500 mg/day	7/3/02-8/21/02	7/5/02-raw throat 7/14/02-“allergy attack”
4	[] 3300 mg/day	6/19/02-8/19/02	6/20/02-nose bleed, thrush 6/22/02-headache 6/27/02-difficulty breathing 6/28/02-right middle lobe “full” started Biaxan, methylprednisone, albuterol 7/10/02-hospitalized due to “continued discomfort” started tobramycin and Zosyn 7/14/02-fever 7/16/02-doctor’s visit due to “problems” 7/17/02-vaginal yeast infection
6	Placebo 5 caps./day	7/1/02-8/21/02	8/15/02-emergency room visit and CT scan for severe headache 8/17/02-nose bleed
8	Placebo 13 caps./day	7/3/02-8/19/02	8/11/02-stomach ache 8/12/02-bloody nose
9	[] 2700 mg/day	7/3/02-8/19/02	7/8/02-headache treated with ibuprofen
12	Placebo 11 caps./day	7/2/02-8/21/02	7/5/02-stomach ache, hard to breathe 7/7/02-fever
14	[] 3300 mg/day	7/1/02-8/2/02	8/18/02-“really sick” and “high fever”
15	[] 1500 mg/day	6/19/02-8/19/02	6/25/02-headache treated with tylenol
16	Placebo 13 caps./day	6/19/02-8/19/02	7/4/02-cold 7/16/02-nose bleed

Subject No.	Treatment Arm	Approximate Treatment Dates	Date of Adverse Event Reported in Patient Diaries
			(date?)-treated with cipro and spironex
17	Placebo 9 caps./day	6/19/02-8/19/02	8/14/02-tonsillitis treated with antibiotics
18	[] 1500 mg/day	6/19/02-8/19/02	8/14/02-behavioral changes 8/15/02-blood in nasal secretions

4) FAILURE TO PROVIDE INFORMED CONSENT DOCUMENT THAT CONTAINS ALL THE BASIC ELEMENTS OF INFORMED CONSENT [21 CFR 50.25(a)].

The informed consent document is required to contain eight basic elements [21 CFR 50.25(a)]. Our investigation found that the informed consent document used in your study did not contain all of the required elements.

- a. You failed to include the expected duration of study participation, description of procedures to be followed, and identification of any procedures which are experimental. For example, the informed consent document did not disclose that the plan was to treat subjects for approximately 5 months (2 months and 2 weeks treatment with a placebo and the same length of time with [] see your Medical Research Proposal dated August 17, 2000. The informed consent document also failed to specify the evaluations that study subjects would be required to undergo, including a physical exam and medical history, pulmonary function testing, oximetry, bacterial culture, and a 6-minute walk test.
- b. You failed to include an explanation in the consent document as to whether any compensation or medical treatments would be available if injury occurs and, if so, what they consist of, and where further information may be obtained.
- c. You failed to include a statement in the consent form that refusal to participate or discontinuation would involve no penalty or loss of benefits to which the subject is otherwise entitled.

5) FAILURE TO DOCUMENT INFORMED CONSENT [21 CFR 50.27(a)].

Informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)]. Our investigation found that you failed to adequately document the informed consent of subjects you enrolled in this study. For example:

- a. You failed to use an informed consent document that was approved by the IRB.
- b. You did not have on file signed and dated informed consent documents for

subjects 6 and 10.

- c. You failed to document the date that informed consent was obtained for any of the subjects enrolled in the study.

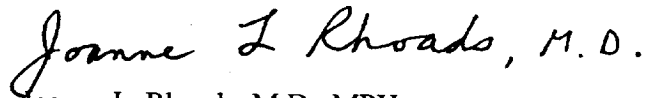
This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you must notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Leslie Ball, M.D., at (301) 827-5455, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,



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